SCHEDULE 1

$$\textbf{Degree of Fluctuation} = \frac{C^{ss}{}_{\max} - C^{ss}{}_{\min}}{C_{avg}} * 100\,\%$$

Where

$$C^{ss}{}_{\max} = \frac{FDose}{V_d}\left(\frac{1}{1-e^{-k\tau}}\right)e^{-kt'_p}, \quad \text{with } t'_p = 2.303 * \log\left(\frac{k_a(1-e^{-k\tau})/k(1-e^{-k_a\tau})}{k_a - k}\right)$$

$$C^{ss}{}_{\min} = \frac{k_a FDose}{V_d(k_a - k)}\left(\frac{1}{1-e^{-k\tau}}\right)e^{-k\tau}$$

$$C_{avg} = \frac{AUC_\tau}{\tau}, \quad \text{with } AUC_\tau = \frac{FDose}{Cl}$$

Since $Cl = kV_d \rightarrow AUC_\tau = \frac{FDose}{kV_d}$

Therefore $C_{avg} = \frac{\left(\frac{FDose}{kV_d}\right)}{\tau}$

F = Fraction Absorbed
k_a = Absorption Rate Constant
k = Elimination Rate Constant
V_d = Apparent Volume of Distribution
Cl = Clearance
τ = Dosing Interval

By substituting the above $C^{ss}{}_{max}$, $C^{ss}{}_{min}$ and C_{avg} equations into the Degree of Fluctuation equation:

$$\textbf{Degree of Fluctuation} = \frac{\left(\frac{FDose}{V_d}\left(\frac{1}{1-e^{-k\tau}}\right)e^{-kt'_p}\right) - \left(\frac{k_a FDose}{V_d(k_a - k)}\left(\frac{1}{1-e^{-k\tau}}\right)e^{-k\tau}\right)}{\frac{\left(\frac{FDose}{kV_d}\right)}{\tau}} * 100\,\%$$

Simplifying the equation → $$\frac{\frac{FDose}{V_d}\left[\left(\frac{1}{1-e^{-k\tau}}\right)e^{-kt'_p}-\left(\frac{k_a}{(k_a-k)}\left(\frac{1}{1-e^{-k\tau}}\right)e^{-k\tau}\right)\right]}{\frac{FDose}{V_d}\left(\frac{1}{k\tau}\right)} * 100\ \%$$

Then cancelling out the term $\frac{FDose}{V_d}$ → $$\frac{\left(\frac{1}{1-e^{-k\tau}}\right)e^{-kt'_p}-\left(\frac{k_a}{(k_a-k)}\left(\frac{1}{1-e^{-k\tau}}\right)e^{-k\tau}\right)}{\left(\frac{1}{k\tau}\right)} * 100\ \%$$

Finally, rearranging the equation further → $$\frac{\frac{1}{1-e^{-k\tau}}\left(e^{-kt'_p}-\frac{k_a}{(k_a-k)}e^{-k\tau}\right)}{\left(\frac{1}{k\tau}\right)} * 100\ \%$$

∴ **Degree of Fluctuation** = $$\frac{\frac{1}{1-e^{-k\tau}}\left(e^{-kt'_p}-\frac{k_a}{(k_a-k)}e^{-k\tau}\right)}{\left(\frac{1}{k\tau}\right)} * 100\ \%$$

CONCLUSION:

- **Degree of Fluctuation is dose independent**
- **Degree of Fluctuation is dependent on absorption and elimination rates and the dosing interval**